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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,932	05/05/2006	Yechezkel Barenholz	BARENHOLZ14	4072

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EXAMINER	
EPPS -SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,932	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-82 and 84-100* is/are pending in the application.

4a) Of the above claim(s) *84-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/15/08;8/11/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-60, 83 and 101-106 are cancelled. Claims 61-82 and 84-100 are pending. Claims 84-100 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/01/2009.

2. Applicant's election of Group I, claims 61-82 in the reply filed on 06/01/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 61-62, and 65-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Barenholz et al. (US2008/0112917A1).

5. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

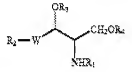
either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

6. The instant claims are drawn to a method for transfecting a cell with a nucleic acid molecule comprising contacting said cell with a sphingoid-polyalkylamine conjugate together with said nucleic acid molecule, wherein said sphingoid-polyalkylamine conjugate comprises a sphingoid backbone carrying, via a carbamoyl bond, at least one polyalkylamine.

7. Barenholz et al. teach the following:

[0047] "The present invention concerns novel lipid-like cationic (LLC) compounds which may be used, inter alia, as capturing agents and in particular, as vehicles for delivering of polynucleotides, oligonucleotides, proteins, peptides and drugs into cells. [0048] The lipid-like cationic compounds have the following general formula (I):

[0019] According to a first of its aspects the present invention provides a sphingoid-polyalkylamine conjugate of the following formula (I):



[0020] wherein

[0021] R_1 represents a hydrogen, a branched or linear alkyl, aryl, alkylamine, or a group —C(O)R_3;

[0022] R_2 and R_4 represent, independently, a branched or linear C_{10}-C_{24} alkyl, alkenyl or polyenyl groups;

[0023] R_3 and R_4 are independently a group —C(O)—NR_6R_7, R_7, R_6 and R_7 being the same or different for R_3 and R_4 and represent, independently, a hydrogen, or a saturated or unsaturated branched or linear polyalkylamine, wherein one or more amine units in said polyalkylamine may be a quaternary ammonium; or R_3 is a hydrogen; or

[0024] R_3 and R_4 form together with the oxygen atoms to which they are bound a heterocyclic ring comprising —C(O)—NR_8—$[R_9$—$NR_9]_m$—C(O)—, R_8 represents a saturated or unsaturated C_1-C_4 alkyl and R_9 represents a hydrogen or a polyalkylamine of the formula —$[R_9$—$NR_9]_n$—, wherein said R_9 or each alkylamine unit R_9NR_9— may be the same or different in said polyalkylamine; and

[0025] n and m, represent independently an integer from 1 to 10; preferably 3 to 6;

[0026] W represents a group selected from —CH═CH—, —CH_2—CH(OH)— or —CH_2—CH_2—;

[0027] as well as salts and stereoisomers of said compound of formula (I).

Barenholz et al. further teaches the following embodiments:

[0052]The term biologically active molecule used herein interchangeably with the term biologically active entity as used herein refers to any biologically active substance having a net negative charge or containing one or more regions or moieties carrying a (local) negative charge, such that under suitable condition it interacts with the net positive charge of the LLC compound of the invention. Non limiting examples of biological entities which may be delivered by the LLC compounds of the invention include: *polynucleotides, oligonucleotides*, proteins, peptides and drugs.

[0053]Interaction or complexation as used herein denotes any type of association known in the art, including electrostatic interaction, or when the LLC compound form micelles and/or vesiculate (e.g. to form liposomes), said association encompass encapsulation of the biological entity within the vesicle, entrapment of the biological entity (in whole or in part) within the lipid-like layer of the vesicle (insertion), electrostatic

adsorption to the surface of *the micelles or the vesicles or any combination of the above*. In the following description, all possible interactions between the LLC compound and the biologically active entity are referred to by the term "complex".

[0054]The possible interactions between the LLC compound and the biologically active entity may be referred to by the general term "complexation". The complexes formed between the LLC compound and the biological entity may be suitable as a delivery system, e.g. for targeting such biological entities into cells.

[0057]Non-limiting examples of the sphingoids or sphingoid bases which may be used in the contents of the present invention include sphingosine, dihydrosphingosine, phytosphingosine, dehydrophytosphinosine and derivatives thereof. *Non-limiting examples of such derivatives include acyl derivatives, such as ceramide (N-acylsphingosine), dihydroceramides, phytoceramides and dihydrophytoceramides as well as ceramines (N-allylsphinogsines) and the corresponding derivatives (e.g. dihydroceramine, phytoceramine, dihydrophytoceramines etc.).*

Barenholz et al. teach each and every aspect of the instant invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 61-62, and 65-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Jorgensen et al. U.S. PreGrant Pub. No. 2002/0188023 A1, published December 12, 2002.

10. Jorgensen et al. teaches a composition comprising lipid-polyalkylamine conjugates. The lipid that Jorgensen et al. teaches is ceramide. [Paragraph 064, in particular.] The polyalkylamine that Jorgensen et al. teaches includes spermine and spermidine. [Paragraph 0053, in particular.] Jorgensen et al. also teaches that the lipid-

polyalkylamine conjugate can be linked using a hydrocarbyl group, including carbamoyl. [Paragraphs 0047 and 0066, in particular.] In the instant case, Jorgensen et al. teaches the claimed sphingoid-polyalkylamine conjugate. Jorgenson also teaches that the compounds of their invention can be used in formulations for gene therapy, which involves introduction of foreign nucleic acid into cells, i.e. transfection, so that its expressed protein may carry out a desired therapeutic function, see paragraph [0002]. Jorgensen et al. teaches that the compounds of their invention alleviate the problems known in the art to be associated with gene delivery vehicles, see paragraphs [0008-0016].

11. In a preferred aspect, Jorgensen et al. discloses a composition comprising an admixture with a condensed polypeptide/nucleic acid complex to provide a non-viral nucleic acid delivery vehicle, paragraphs [0070-0077]. Jorgensen et al. teaches that the compound is a cationic liposome that can be used to facilitate delivery of therapeutic agents such as DNA, mRNA, antisense oligonucleotides, proteins and drugs into cells.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 61-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jorgensen et al. U.S. PreGrant Pub. No. 2002/0188023 A1, or Barenholz et al. (US2008/0112917A1) in view of Wheeler et al. (US 5,976,567)

14. Both Barenholz et al. and Jorgensen et al. teach sphingoid-polyalkyamine conjugates according to the present invention, and nucleic acid compositions comprising said conjugates, as stated above. However, these references do not disclose wherein the nucleic acid is either a plasmid or a siRNA.

15. Wheeler et al. teach lipopolyamine compositions comprising nucleic acid for use in methods involving the transfer of nucleic acid into cells. Wheeler specifically teaches that exogenous nucleic acid such as dsRNA, dsDNA, ssRNA, ssDNA, and cloned DNA in the form of a vector such as a plasmid or viral genome, may be combined in a transfection complex.

16. Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to include plasmid or siRNA nucleic acid with the lipid-polyalkylamine conjugates of either Barenholz et al. or Jorgensen et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to facilitate the delivery of these molecules into cells. One of ordinary skill in the art would have had a reasonable expectation of success for doing so because Jorgensen et al. discloses that lipid-polyalkylamine conjugates are effective to facilitate delivery of drugs into cells. Additionally, one of ordinary skill in the art would have been motivated to make this modification to the teachings of Barenholz et al., since the compounds of Barenholz et al. are disclosed as being useful for the delivery of

polynucleotides and oligonucleotides, and furthermore for use with any biologically active substance having a net negative charge or containing one or more regions or moieties carrying a (local) negative charge, such that under suitable condition it interacts with the net positive charge of the LLC compound of the invention, see ¶ [0052].

17.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633